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Clinical and microbiological characteristics of recurrent group B streptococcal infection among non-pregnant adults

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SUMMARY

Objective: This study aimed to investigate the clinical and microbiological features of recurrent group B streptococcal (GBS) diseases among non-pregnant adults.
Methods: All hospitalized non-pregnant adults who had culture-proven GBS infections between January 2008 and December 2010 were enrolled in this retrospective study. Bacterial isolates were examined for their serotypes, genotypes, and antimicrobial resistance.
Results: The recurrence rate of GBS infection in Taiwan was found to be 9.3%. Of the 70 recurrent episodes in 32 patients, infections of the urinary tract (U) were diagnosed clinically in 55.7%, infections of the soft tissue (S) in 31.4%, and infections of the bloodstream (B) in 12.9%. The initial/recurrent episodes in 25 patients were mainly U/U (40.6%), followed by S/S (18.8%) and B/B (6.2%). The serotypes/serogroups identified were serotypes V (34.3%), Ib (22.9%), VI (17.1%), III (12.9%), IV (7.1%), and Ia (5.7%). Recurrent strains showed less resistance to erythromycin or clindamycin than non-recurrent strains. Six distinct genotypes were identified in 12 serotype VI isolates derived from seven patients; five of these isolate pairs had identical genotypes.
Conclusions: Recurrent GBS diseases were found to occur considerably more often than previously thought, mainly in adults with a high comorbid index. Relapse, not new acquisition, was found to be more common.

1. Introduction

Invasive group B streptococcal (GBS) diseases in non-pregnant adults represent a substantial and increasing health burden worldwide, particularly in the elderly and those with comorbidities.[1–4] Diabetes mellitus, cirrhosis, renal failure, cancer, and decubitus ulcers are independent risk factors for invasive GBS diseases in non-pregnant adults.[4,5] Common clinical presentations in these patients include skin and soft tissue infections, bacteremia, pneumonia, and urinary tract infections.[6] The worldwide development of antimicrobial resistance to macrolides, lincosamides, and fluoroquinolones and the emergence of penicillin resistance in GBS has limited the use of these antibiotics to treat certain infections.[7–9]

The recurrence of GBS infections, first reported in the mid to late 1970s, remains a rare manifestation of pediatric and adult GBS infections.[10,11] Although little is known about this phenomenon, two population-based surveillance studies in Denmark and North America demonstrated the recurrence rate to be 1.3% for children and 4.3% for adults.[11,12] Predicting which patients among those

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with an initial GBS infection will develop disease recurrence is challenging. In fact, patients with recurrent GBS infections clinically resemble patients with their first GBS infection. Data describing the clinical and microbiological features of recurrent GBS infection in adults, including risk factors to predict recurrence, are lacking. Whether a tendency exists in strain-specific characteristics that contribute markedly to recurrence also remains unknown.

This study investigated the clinical characteristics of recurrent GBS infections, specifically with respect to grading systems that accurately predict recurrence. This study also identified the capsular serotypes, resistance phenotypes, and pulsed-field gel electrophoresis (PFGE) genotypes of the clinical isolates causing recurrent infections.

2. Materials and methods

2.1. Patients and isolates

All hospitalized non-pregnant adults who had culture-proven GBS infections between January 2008 and December 2010 were enrolled in this retrospective study. A recurrent GBS infection was defined as a new culture-proven GBS infection that occurred more than 1 month after completion of antimicrobial therapy for the initial infection in the same individual.[13] Patients with nosocomial infections were ineligible when they had hospital-acquired GBS infections. Clinical isolates of GBS were identified by standard laboratory techniques, in accordance with the guidelines of the US Centers for Disease Control and Prevention (CDC; 2010),[14] at the Department of Laboratory Medicine, Chang Gung Memorial Hospital (CGMH), Chiayi, which is a 1300-bed tertiary care teaching hospital located in southern Taiwan. All clinical isolates of GBS were selected using Todd–Hewitt broth (Oxoid, UK) supplemented with colistin (10 μg/ml) and nalidixic acid (15 μg/ml) (bioMérieux, France) in order to prevent growth of contaminants. All suspected GBS colonies (pin point, with narrow beta-hemolysis) were sub-cultured on blood agar and subjected to Gram staining and catalase tests. All Gram-positive and catalase-negative cocci isolates were confirmed using the Christie, Atkins, Munch-Peterson (CAMP) test and latex agglutination assay.[15] This study was approved by the research ethics committee of CGMH. The serotype and serogroup (ST/SG) of each isolate were determined using a multiplex PCR assay, as described previously.[16]

2.2. Clinical information

The medical charts of each patient were reviewed and the following data collected: demographics, comorbid conditions, hospitalization history, definitive antibiotic regimens, duration of antibiotic treatment, final diagnosis, and outcome. The Charlson comorbidity index (CCI) is a weighted-score scale based on the relative risk of 19 conditions that significantly influence outcome.[17] Patients were considered to have a comorbid condition when they had a listed disorder in their records or were treated for the disorder. The CCI scores were calculated by weighting each comorbid disease independently.

2.3. Antimicrobial susceptibility

All isolates were screened for susceptibility to erythromycin and clindamycin using double disk diffusion tests. Macrolide–lincosamide–streptogramin B (MLS_B) phenotypes were characterized as described previously.[18] Macrolide phenotypes (M) were categorized by susceptibility to clindamycin without blunting inhibition zones around the clindamycin disk. The minimum inhibitory concentration (MIC) of dalfopristin was applied to identify the lincosamide–streptogramin A (LSA) phenotypes in isolates with erythromycin susceptibility and clindamycin resistance. Resistance to erythromycin, clindamycin, and dalfopristin was identified using the agar dilution method with the breakpoints of the Clinical and Laboratory Standards Institute.[19]

2.4. DNA preparation and PFGE

Macrofragments of genomic DNA from serotype VI isolates, digested with *Sma*I (New England BioLabs, Frankfurt, Germany), were analyzed by pulsed-field gel electrophoresis (PFGE), as described previously.[20] The total number of visible bands was counted for each isolate, and patterns were compared visually. Genotypes and subtypes were verified using the criteria of Tenover et al.[21]

2.5. Statistical analysis

Categorical data were analyzed using the Chi-square test or Fisher's exact test. Continuous variables were analyzed using the Student's *t*-test. Univariate and multivariate logistic regression analysis was used to discriminate independent risk factors of comorbid conditions. All data were analyzed using IBM–SPSS v. 20.0 software (IBM Corp., Armonk, NY, USA). Two-sided *p*-values <0.05 were considered to be statistically significant.

3. Results

3.1. Demographics

In total, 345 individuals had 383 episodes of GBS infection, and recurrent infections were detected in 32 patients (70 episodes); thus, the recurrence rate was 9.3% (32/345). The mean age of the 345 patients was 57.7 years (range 18–92 years) when they had their first GBS infection (Table 1). No difference in gender distribution was found between the two groups of patients.

3.2. Comorbid conditions

In total, 165 (47.8%) of the 345 patients had a CCI score ≥ 1. The most common comorbid condition encountered in recurrence was diabetes (31.2%), followed by diabetes with end-organ damage (18.8%), peptic ulcer disease (15.6%), any prior tumor (9.4%), and moderate to severe renal disease (9.4%) (Table 1). Although diabetes with end-organ damage was a risk factor for recurrence ($p = 0.012$), multivariate analysis showed that diabetic patients with and without end-organ damage had a higher risk for recurrent infections than non-diabetic patients (16.7% (16/96) vs. 6.4% (16/249); $p = 0.003$) (odds ratio 2.913, 95% confidence interval 1.392–6.092; $p = 0.005$) (data not shown).

The weighted scores of all comorbid conditions were summed and then scaled to the CCI. The mean CCI of recurrence patients was significantly higher than that of non-recurrence patients (1.88 ± 1.91 vs. 1.11 ± 1.58; $p = 0.011$).

3.3. Clinical diagnosis and time intervals

The clinical diagnosis of the 70 recurrent infections was 39 urinary tract infections (55.7%) (U), 22 soft tissue infections (31.4%) (S), and nine bloodstream infections (12.9%) (B) (Table 2). Twenty-five (78.1%) of the 32 patients had similar clinical presentations for consecutive episodes of GBS infection, mainly U/U (40.6%), followed by S/S (18.8%), B/B (6.2%), S/B (6.2%), U/U/U (6.2%), and S/S/S (6.2%). Primary bacteremia was found in patients in the B/B, U/B, and U/U/B groups. Soft tissue infection with bacteremia was categorized into the bloodstream infection (B)

Table 1
Demographics and Charlson comorbidity index (CCI) scores for the 345 patients with GBS infection

	Total, *n* (%) (*N* = 345)	Recurrent, *n* (%) (*n* = 32)	Non-recurrent, *n* (%) (*n* = 313)	*p*-Value
Demographics				
Age, years, mean ± SD	57.7 ± 15.1	59.2 ± 14.3	57.6 ± 15.1	0.568
Male, *n* (%)	115 (33.3)	14 (43.8)	101 (32.3)	0.189
Charlson comorbidity index, *n* (%)				
Diabetes	70 (20.3)	10 (31.2)	60 (19.2)	0.106
Peptic ulcer disease	38 (11.0)	5 (15.6)	33 (10.5)	0.374
Chronic pulmonary disease	29 (8.4)	2 (6.2)	27 (8.6)	0.644
Mild liver disease	20 (5.8)	2 (6.2)	18 (5.8)	0.707
Dementia	15 (4.3)	2 (6.2)	13 (4.2)	0.580
Coronary artery disease	14 (4.1)	2 (6.2)	12 (3.8)	0.379
Cerebrovascular disease	13 (3.8)	1 (3.1)	12 (3.8)	1.000
Congestive heart failure	4 (1.2)	1 (3.1)	3 (1.0)	0.324
Connective tissue disease	4 (1.2)	1 (3.1)	3 (1.0)	0.324
Peripheral vascular disease	1 (0.3)	0 (0.0)	1 (0.3)	1.000
Any prior tumor (within 5 years of diagnosis)	27 (7.8)	3 (9.4)	24 (7.7)	0.728
Diabetes with end-organ damage	26 (7.5)	6 (18.8)	20 (6.4)	0.012
Moderate to severe renal disease	18 (5.2)	3 (9.4)	15 (4.8)	0.227
Hemiplegia	3 (0.9)	1 (3.1)	2 (0.6)	0.254
Leukemia	0 (0.0)	0 (0.0)	0 (0.0)	
Lymphoma	1 (0.3)	1 (3.1)	0 (0)	0.093
Moderate to severe liver disease	13 (3.8)	2 (6.2)	11 (3.5)	0.344
Metastatic solid tumor	2 (0.6)	0 (0.0)	2 (0.6)	1.000
AIDS (not only HIV-positive)	0 (0.0)	0 (0.0)	0 (0.0)	
Total of CCI (mean)	1.2 ± 1.6	1.9 ± 1.9	1.1 ± 1.6	0.011

GBS, group B Streptococcus; SD, standard deviation.

Table 2
Clinical diagnosis and time intervals between consecutive infections in 32 patients with 70 episodes of infection

	Diagnosis of consecutive episodes[a] (*n* = 32 patients; 70 episodes)											Time intervals (days)
	U/U	S/S	B/B	S/B	S/U	U/B	U/S	U/U/U	S/S/S	U/U/B	B/U/U	
Total (*n* = 32; 70 episodes)	13 (40.6)	6 (18.8)	2 (6.2)	2 (6.2)	1 (3.1)	1 (3.1)	1 (3.1)	2 (6.2)	2 (6.2)	1 (3.1)	1 (3.1)	91.0 ± 96.1
Concordant serotype (*n* = 26; 57 episodes)	9 (34.6)	6 (23.1)	2 (7.7)	1 (3.8)	1 (3.8)	1 (3.8)	1 (3.8)	2 (7.7)	2 (7.7)	1 (3.8)	0 (0.0)	76.2 ± 84.6
Discordant serotype (*n* = 6; 13 episodes)	4 (66.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	156.4 ± 122.5
p-Value	0.194	0.564	1.000	0.345	1.000	1.000	1.000	1.000	1.000	1.000	0.188	0.044

[a] U, urinary tract infection; S, soft tissue infection; B, bloodstream infection.

group; bacteremia in two patients in the S/B group originated from a soft tissue infection. No deep tissue infection such as necrotizing fasciitis was found in the soft tissue infection (S) group.

The length of definitive antimicrobial treatment (penicillins or cephalosporins), depending on the infection type, was 7–36 days (median 17 days) for the first infection (18 U, 11 S, and 3 B), 6–29 days (median 13 days) for the second infection (18 U, 9 S, and 5 B), and 7–30 days (median 14 days) for the third infection (3 U, 2 S, and 1 B).

For the 38 time intervals between consecutive episodes of disease recurrence, the mean duration of the time intervals was 90.97 ± 96.08 days (range 32–384 days). Concordant ST/SG, responsible for 81.3% (26/32) of recurrent infections, had a significantly shorter time interval than discordant ST/SG (76.19 ± 84.62 days vs. 156.43 ± 122.46 days; $p = 0.044$).

3.4. Serotype/serogroup

Regarding the 383 isolates, the prevalence of ST/SGs was as follows: V 29.5%, Ib 23.8%, III 15.1%, VI 9.4%, IV 8.6%, Ia 5.0%, II 3.9%, non-typeable 3.7%, and VII 1.0% (Table 3). Likely due to small numbers of isolates, serotypes II, VII, and the non-typeable were not identified in recurrent strains. Recurrence was not correlated with any specific ST/SG, except that serotype VI accounted for 17.1% of recurrent strains and 7.7% of non-recurrent strains ($p = 0.014$).

3.5. Resistance phenotypes and genotype analysis

All clinical isolates remained susceptible to penicillin; however, 59.8% (229/383) and 59.3% (227/383) of isolates had resistance to erythromycin and clindamycin, respectively (Table 4). Somewhat surprisingly, recurrent strains had a lower rate of resistance to erythromycin or clindamycin (51.4%) than non-recurrent strains (66.1%) ($p = 0.021$). Analysis of resistance phenotypes among the 243 resistant strains of recurrent and non-recurrent origin indicated that the MLS_B phenotype accounted for 55.6%, the M phenotype for 4.2%, and the LSA phenotype for 3.7%. Moreover, M phenotype and LSA phenotype were not detected in recurrent strains.

This study applied *SmaI*-digested PFGE analysis to the 12 strains of serotype VI (derived from seven individuals with recurrent infection). These patients were classified into three major genotypes containing six subtypes, each comprising eight or nine fragments ranging from approximately <48.5 kb to 533.5 kb (Figure 1). Specifically, five isolate pairs from five individuals (patients 1–5) had the same genotype. Of the remaining two

Table 3
Distribution of GBS capsular serotypes of 383 isolates collected from 345 patients with GBS infection

	Serotype								
	Ia	Ib	II	III	IV	V	VI	VII	Non-typeable
Total isolates (*n*; % of 383)	19 (5.0)	91 (23.8)	15 (3.9)	58 (15.1)	33 (8.6)	113 (29.5)	36 (9.4)	4 (1.0)	14 (3.7)
Recurrent (*n*; % of 70)	4 (5.7)	16 (22.9)	0 (0.0)	9 (12.9)	5 (7.1)	24 (34.3)	12 (17.1)	0 (0.0)	0 (0.0)
Non-recurrent (*n*; % of 313)	15 (4.8)	75 (24.0)	15 (4.8)	49 (15.7)	28 (8.9)	89 (28.4)	24 (7.7)	4 (1.3)	14 (4.5)
p-Value	0.761	0.844	0.084	0.555	0.627	0.332	0.014	1.000	0.083

GBS, group B Streptococcus.

Table 4
Prevalence of resistance phenotypes of 383 isolates collected from 345 patients with GBS infection

	Susceptibility to erythromycin/clindamycin (resistance phenotypes)			
	R/R (MLS_B phenotype)[a]	R/S (M phenotype)[b]	S/R (LSA phenotype)[c]	S/S
Total (*n*; % of 383)	213 (55.6)	16 (4.2)	14 (3.7)	140 (36.6)
Recurrent (*n*; % of 70)	36 (51.4)	0 (0.0)	0 (0.0)	34 (48.6)
Non-recurrent (*n*; % of 313)	177 (56.5)	16 (5.1)	14 (4.5)	106 (33.9)
p-Value	0.436	0.051	0.083	0.021

GBS, group B Streptococcus; R, resistant; S, susceptible.
[a] MLS_B: macrolide–lincosamide–streptogramin B.
[b] M: macrolide.
[c] LSA: lincosamide–streptogramin A.

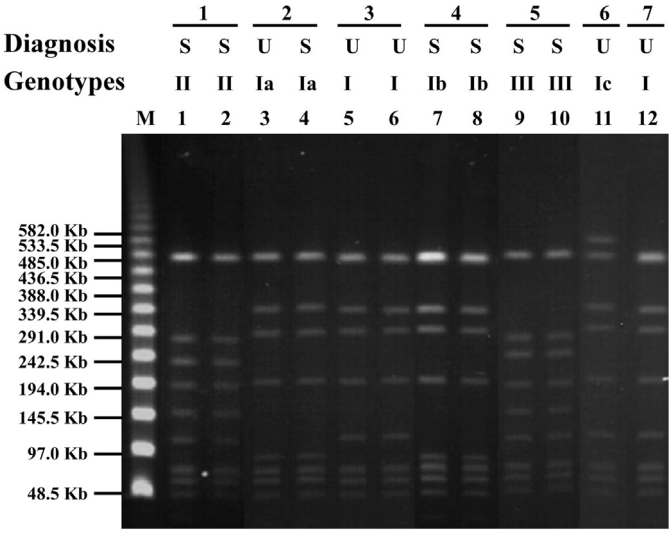

Figure 1. PFGE analysis of 12 strains of serotype VI (derived from seven individuals with recurrence). M: lambda ladder marker; lanes 1–12: strains 58, 59, 443, 447, 292, 405, 489, 491, 419, 427, 219, and 431. S: soft tissue infection; U: urinary tract infection; B: bloodstream infection. Pulsotype: three major genotypes (I–III) contained a total of six subtypes, each comprising eight or nine fragments ranging from approximately <48.5 kb to 533.5 kb. Five isolate pairs belonging to five individuals (patients 1–5) were genotypically identical.

patients (patients 6 and 7), clinical diagnoses and ST/SG in consecutive infections were U/U (III/VI) and U/U (VI/V), and time intervals were 163 days and 32 days, respectively.

4. Discussion

Until recently, little data existed in terms of risk factors for recurrent GBS infection among adults, although diabetes mellitus, cirrhosis, and renal failure have each been associated with a single GBS infection in some population-based studies.[4] Patients who suffered from recurrent GBS infection in this study were likely to have diabetes, a peptic ulcer, chronic pulmonary diseases, any prior tumor, and diabetes with end-organ damage. Diabetes with or without end-organ damage is an independent risk factor for recurrence, as it was for the initial GBS infection.[4,5] Nevertheless, no clinical features were identified in this study that could be used to distinguish those patients with recurrence from those who do not develop a recurrent infection. Even if diabetes with or without end-organ damage is the best clinical clue for identifying patients likely to develop recurrence, the common occurrence of diabetes and the low rate of recurrent GBS infection in the community limits its predictive value.

Analytical results showed a substantially higher CCI score in patients with a recurrent infection than in patients without a recurrent infection, suggesting that the CCI predicts the recurrence of GBS infection better than individual comorbidity conditions. Physicians must pay special attention to those patients who have one episode of GBS infection and a high CCI score because they are at higher risk of recurrence. This is the first report to specifically validate the use of the CCI to predict the recurrence of GBS infection.

In a national survey of non-pregnant adults with a single GBS infection, the most common clinical diagnosis was skin, soft tissue, and bone infections (36%), followed by bacteremia (30%), urinary tract infections (14%), pneumonia (9.5%), and peritonitis (7.3%).[2] This study showed that nearly half of the recurrent infections were urinary tract infections (55.7%, 39/70 episodes), mainly U/U (40.6%, 13/32 patients). Despite the limited number of cases, the results suggest that GBS is a uropathogen and that GBS can cause a recurrent urinary tract infection by unknown mechanisms.[22]

Several investigations have demonstrated the time to second infection to be short when recurrent infection is caused by the same serotype responsible for the first infection.[10,11] Data in this study are in agreement with those reported in the aforementioned studies; concordant serotypes were often isolated from patients whose initial infection was relatively recent (mean interval between the initial and recurrent infection was 76.2 days), whereas discordant serotypes were identified in those with a longer interval between the two infections (mean duration 156.4

days). This finding is notable because a short interval between consecutive infections may imply a relapse of the first infection.

From the analytical results, we speculate that the second infections were most often attributable to either incomplete treatment of the initial infection or treatment failure. In fact, each patient in this study was given antimicrobial therapy with what is now considered, depending on the infection type, an appropriate drug, dosage, and duration. Regimens (penicillins or cephalosporins) as well as the duration (7–36 days) of antimicrobial therapy for patients with an initial infection was likely adequate for symptom relief, but not necessarily for eradication, resulting in subsequent relapse. The extension of therapy beyond the currently recommended duration for GBS infection in an attempt to eradicate the infection is not recommended. Thus, GBS eradication in high-risk patients with GBS infection remains challenging.[23]

At least nine recognizable serotypes (Ia, Ib, and II–VIII) exist in GBS, and serotype IX has recently been identified.[24] The prevalent ST/SG of GBS causing invasive infection usually varies over time and among different populations.[4,6] Since 1996, serotype V has been the predominant serotype (29.0–47.7%) for non-pregnant adults in North America, Asia, and Africa who have a single GBS infection.[25–27] In Taiwan, type V (27.1–32.5%) and type III (20.0–28.5%) are the most widespread ST/SGs of GBS.[26,28,29] Consistent with previous surveillance data, serotype V accounted for 34.3% of serotypes in recurrent strains and 28.4% in non-recurrent strains in this study. A striking finding was the high prevalence of serotype Ib in both recurrent (22.9%) and non-recurrent strains (24.0%); this serotype is currently rare in North America and Europe.[2,3,12] Based on a prior investigation, this remarkable increase in serotype Ib is likely correlated with clonal spread in Taiwan.[30]

This investigation is unique in that a limited number of ST/SGs were found to be disproportionately associated with disease recurrence; serotype VI, for example, was typically associated with recurrent infection. This implies that serotype VI may be more virulent than other serotypes. Further epidemiological studies are needed to determine whether this ST/SG distribution of GBS is restricted to Taiwan.

Despite the wide use of penicillin-based regimens, GBS isolates are usually susceptible to penicillin.[8] However, resistance to antimicrobials used as alternative therapy, especially macrolides, lincosamides, and fluoroquinolones, has been documented increasingly.[7,9] In the USA, recently published data on GBS bacteremia in adults during 2002 to 2010 revealed that erythromycin and clindamycin resistance occurred in 43.6% and 39.7% of cases, respectively.[31] The high prevalence of resistance to erythromycin and clindamycin (59.8% and 59.3%, respectively) in this study was very similar to that reported in a prior survey (58.3% and 57.9%, respectively) from Taiwan for the period 2006–2008.[30]

Conversely, this study showed that recurrent strains typically had a lower rate of resistance to erythromycin or clindamycin. Genetic changes that account for antibiotic resistance in microorganisms also alter virulence to some degree.[7,32,33] Thus, we speculate that non-resistant recurrent strains might be more prone to acquiring virulence traits which may be a survival advantage to microorganisms.[34–36]

The MLS_B phenotype was the predominant resistance phenotype found in recurrent and non-recurrent strains. Genotyping highlighted the fact that ribosomal modification by methylases, encoded by *erm* genes, plays a major role in macrolide resistance for GBS in Taiwan. This observation differs from results reported in England and Wales and North America,[37,38] in which M resistance mechanisms were found, usually involving drug efflux by membrane-bound protein encoded in *mef* genes.

Considerable variation in genetic content was found to exist among strains of serotype VI, implying that the increase in serotype VI in recurrent strains was not due to the dissemination of a few clones in Taiwan. This observation is of epidemiological significance. Further surveillance of clonal heterogeneity in GBS isolates by different measures is necessary. On the other hand, serotyping and genotyping of GBS strains confirmed that the recurrent GBS infection in five of the seven patients was caused by the same strain and not a newly acquired strain. Recurrent GBS infection due to bacterial reinvasion from a colonizing site has been identified in a few studies, although most were limited to pregnant women or neonates.[10,39,40] Harrison et al. (1995), using restriction endonuclease analysis of chromosomal DNA, first determined that 13 of 18 adults were infected by concordant ST/SGs and also genotypically identical GBS strains.[11] Data in this study suggest that recurrent GBS infection should result from relapse of a previous infection.

This study has several limitations. First, it had a cross-sectional design. The 9.3% recurrent infection rate in this hospital-based survey exceeds rates previously reported. The rates of recurrence may increase steadily over time in a longitudinal study. Thus, the cumulative incidences of recurrent GBS infection may be underestimated in this cross-sectional study. The second limitation is that the isolates examined were not population-based and, therefore, may not reflect collective bias. Thirdly, there is a possibility of potential misclassification bias as patients with recurrence may not have attended the same hospital, or patients may not have been hospitalized for the first episode and thus not classified as recurrences.

This snapshot of recurrent GBS infections showed that they occur more frequently than previously thought, despite appropriate antimicrobial therapy, mainly in adults with a high comorbidity index. This is the first study to systematically examine the host- and strain-specific characteristics of recurrent GBS infections. The results indicate that relapse is the major cause of disease recurrence. The development of new treatment modalities to eradicate site-specific colonization, thereby preventing future relapse, would benefit patients.

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Conflict of interest: The authors declare that they have no competing interests.

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